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Perturbations of the Immune System by Xenobiotics

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Classically, immunotoxicology has been defined as the study of adverse effects on the immune system associated with exposure to environmental chemicals, pharmacologic agents, and biologicals. Although a multitude of immune system defects may occur, these can be generally categorized as immunomodulation (immune suppression or potentiation), hypersensitivity (i.e., allergy), and autoimmunity. We present here a brief synopsis of the ontogeny of immunotoxicology as a discipline including methodology currently used in our laboratory, as well as in others, for investigating the immunomodulatory potential of chemicals at the cellular and biochemical level. Additionally, we summarize some studies related to the immunosuppressive effects of one particular compound, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD). Last we discuss potential future directions and challenges in the field of immunotoxicology.

Background

Immunotoxicology can be defined as the study of the adverse effects of environmental chemicals, certain therapeutics, and biologicals on the immune system. The adverse effects that may occur include immunomodulation (i.e., suppression or potentiation), hypersensitivity (i.e., allergy), and, in rare instances, autoimmunity. Although chemical-induced autoimmune diseases are not well documented, the extent of chemical-induced hypersensitivity has been known for a long time (*1,2*). Some of the industrial materials with known or presumed allergic etiology are shown in Table 1. More recently, a large body of information has also developed demonstrating that exposure to certain chemicals or drugs can produce immunosuppression in experimental animals (Table 2) (*3-5*). In contrast to immunosuppressive drugs, however, only a limited number of reports indicate immune dysfunction following a human exposure to chemical xenobiotics.

The sensitivity of the immune system to these chemicals is probably due as much to the general properties of the xenobiotic (e.g. reactivity with macromolecules) as to the complex nature of the immune system, which encompasses antigen recognition and processing; cellular interactions involving cooperation, regulation, and amplification; cell activation, proliferation, and differentiation; and mediator production. The immunosuppressive effects associated with exposure to xenobiotics are often accompanied by increased susceptibility to challenge with infectious agents or tumor cells. Although only limited studies in humans have been conducted, effects similar to those observed in rodents have been reported in several instances following therapeutic, inadvertent, or occupational exposure to xenobiotics exemplifying characteris-

Table 1. Industrial materials known or presumed to cause allergic problems.[a]

Material	Industry
Platinum salts	Metal-refining
Cotton dusts	Textile
Castor bean, green coffee bean papain, pancreatic extracts, organic dusts, and molds	Oil and food
Formaldehyde	Garment, laboratory
Grain and flour	Farmers, bakers, and mill operators
Hog trypsin, ethylenediamine phthalic anhydride, beryllium trimellitic anhydride, and diisocyanates (TDI, HDI, and MDI)	Chemical, plastic, rubber, and resin
Phenylglycine acid chloride, sulfone chloramides, ampicillin, spiramycin, piperazine, amprolium hydrochloride, and antibiotic dust	Pharmaceutical
Wood dusts	Wood mills, carpenters
Vegetable gums (acacia, karaya) and natural resins	Printers
Organophosphate insecticides	Farmers
Pyrolysis products of polyvinyl chloride and label adhesives	Meat wrappers

[a]Modified from Luster and Dean (*2*).

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Table 2. Examples of immunological abnormalities associated with chemical exposure in rodents and humans.

Chemical class	Example	Laboratory immune abnormality	Human immune abnormality[a]
Polyhalogenated aromatic hydrocarbons	TCCD	+	±
	PCB	+	+
	PBB	+	+
	HCB	+	NK
Heavy metals	Lead	+	−
	Cadmium	+	−
	Methyl mercury	+	−
Aromatic hydrocarbons (solvents)	Benzene	+	+
	Toluene	+	+
Polycyclic aromatic hydrocarbons	DMBA	+	NK
	BaP	+	NK
	MCA	+	NK
Pesticides	O,O,S-TMP	+	NK
	Carbofuran	+	NK
	Chlordane	+	NK
Organotins	DOTC	+	NK
	DBTC	+	NK
Aromatic amines	Benzidine	+	+
Oxidant gases (air pollutants)	NO_2	+	NK
	O_3	+	+
	SO_2	+	NK
Others	Asbestos	+	+
	DMN	+	NK

[a]NK not known; ±, positive and negative findings have been reported.

tics of secondary immunodeficiency disease. Among these effects include altered immune responses in Michigan residents and farmers exposed to polybrominated biphenyls (PBBs) through the consumption of contaminated livestock and dairy products (*6*); Chinese and Japanese exposed to polychlorinated biphenyls (PCBs) and dibenzofurans through contaminated rice oil used in cooking (*7*); Spanish residents exhibiting "toxic oil syndrome" following ingestion of isothiocyanate-derived imidazolidinethione adulterated rapeseed oil (*8*); factory workers with aplastic anemia and leukemia occupationally exposed to benzene (*9*); and AIDS patients who develop myelotoxicity following azidothymidine (AZT) therapy (*10*).

Increased susceptibility to infectious disease and neoplasia has been a recurring consequence of chronic immunosuppression or aberrant lymphoid cell differentiation in several of these cohorts. For example, the frequency of neoplasia among Michigan PBB-cohort members exhibiting immune dysfunction is approximately 15-fold greater than that observed in the control Wisconsin farmer cohort (J. G. Bekesi, personal communication). These concerns are also supported by the side effects associated with the therapeutic use of chemical immunosuppressants that are used to treat certain autoimmune, collagen-vascular, and chronic inflammatory diseases, as well as to prevent rejection of transplanted organs. For example, therapeutic immunosuppression frequently causes complications from bacterial, viral, fungal, and parasitic infections.

Another complication of immunosuppression in transplant patients has been a high frequency of secondary cancers (*11*). Partial or complete regression of the secondary cancers often occurs if the therapy is terminated. In a large sampling of renal transplant patients who survived 10 years, approximately 50% developed cancer. The types of tumors observed were heterogenous and included skin and lip cancer (21-fold increase over the general population), non-Hodgkin's lymphomas (28- to 49-fold increase), Kaposi's sarcoma (400- to 500-fold increase), and carcinomas of the cervix (14-fold increase). These examples suggest that perturbations in the immune system may be associated with a wide spectrum of diverse pathologic conditions, some of which may only become detectable after a long latency. However, whether exposure to xenobiotics present in the environment influences immunocompetence of the general population under normal circumstances is not known and remains a central question.

Methodology

The immune system is a complex network comprised of several cell types (i.e., lymphocytes, macrophages, granulocytes, and natural killer cells) whose variety of functions include maintaing homeostasis and health. The mode of its activity resembles that of the endocrine system in that circulating cellular and soluble components can act at sites far removed from their point of origin. The system continuously undergoes proliferation and differentiation. Its primary responsibility is the defense against invasion by pathogenic microbial agents and spontaneously arising neoplasms. In doing so, the intensity and specificity of the immune response must be highly regulated and capable of discerning self from nonself.

Since the immune system is a complex organization of cells with a variety of functions, appropriate evaluation of chemical-mediated effects necessitates the examination of multiple immune functions. One of the focuses among immunotoxicologists has been the development and implementation of a tiered panel of assays to identify im-

Table 3. Panel for detecting immune alterations following chemical or drug exposure in rodents.[a]

Parameter	Procedures
Screen (Tier I)	
Immunopathology	Hematology: complete blood count and differential
	Weights: body, spleen, thymus, kidney, liver
	Cellularity: spleen
	Histology: spleen, thymus, lymph node
Humoral-mediated immunity	Enumerate IgM antibody plaque-forming cells to T-dependent antigen (SRBC); LPS mitogen response
Cell-mediated immunity	Lymphocyte blastogenesis to mitogens (Con A) and mixed leukocyte response against allogeneic leukocytes
Nonspecific immunity	Natural killer (NK) cell activity
Comprehensive (Tier II)	
Immunopathology	Quantitation of splenic B- and T-cell numbers
Humoral-mediated immunity	Enumeration of IgG antibody response to SRBCs
Cell-mediated immunity	Cytotoxic T-lymphocyte (CTL) cytolysis; delayed hypersensitivity response (DHR)
Nonspecific immunity	Macrophage function [quantitation of resident peritoneal cells and phagocytic ability (basal and activated by MAF)]
Host resistance challenge	Syngeneic tumor cells
Models (end points)[b]	PYB6 sarcoma (tumor incidence)
	B16F10 melanoma (lung burden)
	Bacterial models
	Listeria monocytogenes (mortality)
	Streptococcus species (mortality)
	Viral models
	Influenza (mortality)
	Parasite models
	Plasmodium yoelli (Parasitemia)

[a]The testing panel was developed using $B6C3F_1$ female mice.
[b]For any particular chemical being tested, only two or three host resistance models are examined.

munosuppression or enhancement. The National Toxicology Program (NTP) at the National Institute of Environmental Health Sciences (NIEHS) uses a flexible testing panel composed of two tiers (Table 3). This testing configuration has undergone a 4-year developmental and interlaboratory validation period (*12*) and is now routinely used to evaluate the potential of therapeutic or environmental chemicals to modulate immune function in mice. Immune testing configurations have also been described in rats (*13,14*).

The assays listed under Tier I represent a simple screen and include measurements for cell-mediated immunity (CMI), humoral-mediated immunity (HMI), and natural killer (NK) cell activity, as well as immunopathology, the latter of which is part of the standard protocol in subchronic studies conducted by the NTP. The likelihood of detecting potent immunotoxicants using Tier I is high, but will decrease for weaker immunotoxicants, such as those that affect only a specific cell population or subpopulation. Nonetheless, based upon the data from compounds that have completed both Tier I and II testing, no compound has been found to affect an assay in Tier II without demonstrating some effect on Tier I.

The assays listed in Tier II, which allow more flexibility than Tier I, represent a more comprehensive evaluation of the immune system, more likely to identify affected cell types. Criteria usually fulfilled prior to initiating tests in Tier II include lack of overt toxicity at doses where altered immune function(s) are observed in Tier I and evidence that immunotoxicity occurs at relevant dose levels. With pharmaceuticals, this relates to the anticipated therapeutic dose, while with environmental chemicals, this would depend on the anticipated or documented human exposure levels. Evidence of a dose-response relationship would also be an important prerequisite for proceeding to Tier II. The types of assays used in Tier II include quantitation of splenic B- and T-cells, including subpopulations, secondary (IgG) antibody responses, T-cell effector function, and macrophage activity, as well as resistance to challenge with tumor cells or infectious agents.

Regarding CMI, we have examined both delayed hypersensitivity responses (DHRs) and cytotoxic T-lymphocyte (CTL) activity, and accumulating evidence indicates that the latter provides more sensitivity and reproducibility for assessing chemical-induced immunotoxicity. The use of multiple assays in a testing configuration allows the establishment of an immune profile similar to that used to diagnose primary or acquired immunodeficiency diseases. Because of the variability in some of the immune responses, an alteration in a single parameter is normally insufficient to label a compound as immunotoxic. Details describing these methodologies are published elsewhere (*12,15*).

Host resistance models were developed to evaluate the relationship between the immune function tests and more biologically relevant end points (*16,17*). This was particularly important if the immunological data are to be used in risk assessment evaluation. The host resistance models listed in Table 3 have been correlated with immune function assays using data from animals exposed to approximately 15 chemicals over a 4-year period (Table 4). In general, changes in specific immune functions correlated with certain host resistance assays. For example, in-

creased suppression of the antibody plaque-forming cell response and proliferative response to lipopolysaccharide were accompanied by increased susceptibility following challenge with influenza virus and mouse malaria (Plasmodium), agents in which resistance is mediated, at least in part, by antibody. The correlation observed between functional measurements and challenge models, albeit preliminary, attempts to provide insight into the biological significance of the various measures of immune function studied. This type of analysis should provide a better understanding of the relevant immune effector mechanism(s) involved in host resistance, as well as the degree of suppression of immune function necessary to alter host resistance (i.e., functional reserve). Additional qualitative and quantitative information in this area should also improve the accuracy with which the effects of chemicals or drugs on the immune system can be predicted.

Immunotoxic Xenobiotics

Of the list of immunotoxic compounds shown in Table 2, one of the most extensively studied classes of environmental chemicals examined for immunotoxicity in experimental animals or humans is the halogenated aromatic hydrocarbons (HAHs), and, in particular, polychlorinated biphenyls (PCBs), polybrominated biphenyls (PBBs), dibenzo-*p*-dioxins, and dibenzofurans. Despite the species variability associated with the toxicity of these compounds, studies in laboratory animals exposed during neonatal or adult life with HAHs and, in particular, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), have indicated that the immune system is one of the most sensitive targets for toxicity (*5,18–20*). In mice, TCDD causes thymic atrophy, myelotoxicity, inhibition of the complement system, suppression of lymphocyte functions, and increased susceptibility to challenge with infectious agents or transplantable tumor cells. In contrast, NK cell activity and macrophage functions appear spared. The type of effect observed is dependent, to a large extent, on the age of the animal at the time of exposure.

Following perinatal or, in some cases, chronic exposure, the primary immune effects are associated with thymic atrophy and suppression of cell-mediated immunity that mimics neonatal thymectomy. Altered differentiation of intrathymic precursor cells, as occurs following neonatal thymectomy, has not been evaluated following perinatal TCDD exposure. However, T-cells from treated mice demonstrate altered homing patterns (*19*), a feature characteristic of undifferentiated T-cells. Furthermore, *in vitro* studies using a thymocyte and thymic epithelial cell coculture system have shown that pretreatment of thymic epithelial cell monolayers with TCDD inhibits their ability to stimulate T-cell differentiation (*21*). With the use of murine bone-marrow chimeras, it has been shown that inhibition of CTLs by subchronic TCDD exposure is due to the *Ah* genotype of the host and not of the grafted stem cell, further supporting involvement of a secondary tissue (*22*). In contrast to subchronic or perinatal exposure, acute exposure of adult rodents to HAHs has its major effect on rapidly proliferating cell populations, including hematopoietic stem cells and B-lymphocytes, the effect manifested as suppressed antibody responses. Unlike CMI, TCDD inhibits hematopoiesis and B-cell function by directly inhibiting maturation of the B-lymphocytes or bone marrow stem cell.

Myelotoxicity, thymic atrophy, and immunosuppression by TCDD and PCBs appear to be associated with stereospecific binding to the *Ah* receptor, which is present at low concentrations in both lymphoid tissue and lymphoid cells (*5*). This has been supported in genetic studies using *Ah*-responsive and -nonresponsive mouse strains, including mouse strains congenic at the *Ah* locus, where the immunotoxic effects of TCDD segregate with the *Ah* genotype. This can be seen in Figure 1, where a dose-dependent suppression of the antibody response to trinitrophenylated-lipopolysaccharide antigen occurred when purified splenic B-cells obtained from *Ah*-responsive mice were cultured with TCDD, but not when TCDD was cultured with cells from the nonresponsive strain. In contrast, dexamethasone, another potent immunosuppressant that acts via a steroid receptor mechanism, did not show these strain differences. In addition to genetic studies, structure-activity studies showed that the binding affinity of various HAH congeners to the *Ah* receptor correlates with their potency to induce immunosuppression.

Although immunotoxicity by HAHs is mediated through binding to the *Ah* receptor, the mechanisms responsible for toxicity following interaction of the receptor-ligand complex with the *Ah* locus are unknown. In fact, additional loci may be involved, as certain tissue-

Table 4. Correlation between host susceptibility and depressed immune function.[a]

Challenge model	NK cytotoxicity	Proliferation		Antibody		
		MLR	PHA	LPS	PFC	DHR
PYB6 sarcoma	0.45[b] *	0.46*	0.20	0.02	0.22	0.61*
B16F10 melanoma	0.54*	0.02	0.15	0.16	0.15	ND
Listeria	0.01	0.47†	0.37*	0.08	0.01	0.19
Influenza	0.11	0.78*	0.03	0.70*	0.83†	ND
Plasmodium	0.24	0.59	0.67*	0.64*	0.78†	ND

[a]Abbreviations: MLR, mixed lymphocyte reaction; PHA, phytohemagglutinin; LPS, lipopolysaccharide; PFC; DHR, delayed hypersensitivity response; ND, not done.
[b]Correlation coefficient as determined by Spearman's Rank Correlation Test (rho values).
* Significant correlation at $p < 0.05$.
† Significant correlation at $p < 0.01$.

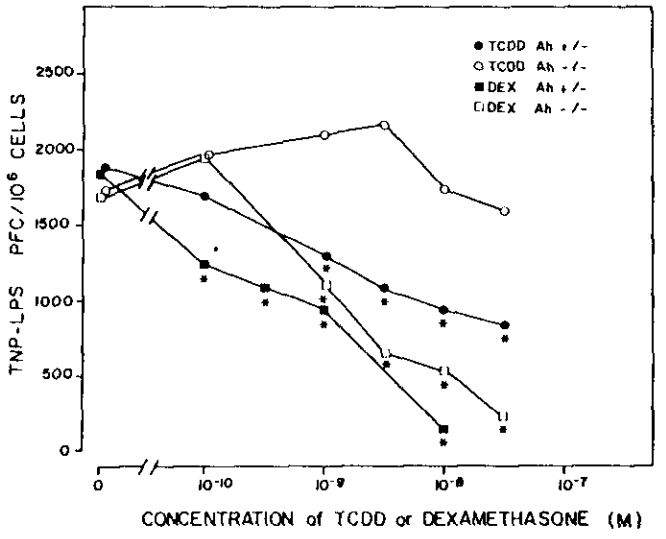

FIGURE 1. Effect of TCDD or dexamethasone (DEX) on TNP-LPS plaque-forming cells from B-cells obtained from *Ah* responsive B6C3F$_1$ and *Ah*-nonresponsive DBA mice. B-cells were cultured in the presence of TCDD or dexamethasone plus TNP-LPS for 4 days and assayed for plaque forming cells using TNP-coupled SRBCs. Asterisk (*) denotes significantly different from vehicle response at $p < 0.05$. From Luster et al. (*24*).

specific responses, such as epidermal hyperplasia in hairless mice, appear to be regulated by at least two genetic loci, *Ah* and *hr* (*23*). Immunosuppression by TCDD does not occur via a cellular depletion mechanism or qualitative and/or quantitative changes in regulatory products, as has been shown to occur with corticosteroids (*5,18*). In epidermal cell lines, TCDD alters normal patterns of proliferation and/or differentiation. Likewise, it has been proposed that TCDD induces similar effects in thymic epithelial cells and lymphocytes. For example, TCDD causes terminal differentiation of thymic epithelial cells (*21*) and blocks the terminal differentiation of murine B-lymphocytes into plasma cells (*24*). This latter effect is associated with qualitative and quantitative changes in phosphorylated proteins that are related to growth promoting activity (i.e., tyrosine kinase) (Clark and Luster, in preparation). Thus, existing data indicate that TCDD immunotoxicity results from altered patterns of cell proliferation and differentiation in distinct lymphoid targets.

Conclusions and Future Direction

The immune system is composed of several cell populations where maturation of each population is subject to orderly control by endogenous hormones and exogenous bacterial products. These mediators possess activation, growth-promotion, and/or differentiation properties, and are under the influence of potent, but not well-understood regulators. From observations in rodents and limited studies in humans inadvertently exposed, it is apparent that a number of xenobiotics adversely affect the immune system. This can occur through disruption of cell maturation or regulation, as well as through cytotoxic processes. These examples, combined with our current knowledge about the pathogenesis of disease, support the possibility that chemical-induced damage to the immune system may be associated with a wide spectrum of diverse pathological conditions, some of which may only become detectable after a long latency. Likewise, exposure to immunotoxic xenobiotics might represent additional risks to individuals with already fragile immune systems (e.g., malnutrition, infancy and old age). However, it is important that caution be exercised when attempting to extrapolate meaningful conclusions from experimental data or isolated epidemiological studies to risk assessment for low-level human exposure.

Because of the functional heterogeneity of the immune system, efforts to assess chemical-induced immunotoxicity in laboratory animals and humans have historically been performed using a tiered approach with multiple assays. A similar configuration as described here has recently been included in EPA's Federal Insecticide, Fungicide and Rodenticide Act regulations for immunotoxicity testing of biochemical pesticides. The value of incorporating immunological rodent data for the toxicological assessment of drugs, chemicals, and biologicals for human risk assessment has been increasingly accepted. The preceding decade of research has provided a data base of immunotoxic and nonimmunotoxic compounds, studies correlating immune dysfunction and altered host resistance, and a better standardized panel of methods for detecting immunomodulatory chemicals. In the near future, research related to methodology is needed to further refine and validate immune function tests and host resistance assays, particularly in the rat; develop, refine, and validate better testing methods to evaluate the effects of chemical inhalation on lung immunity; determine the need and relevance of methods for assessing hematopoietic and polymorphonuclear leukocyte functions; develop and evaluate *in vitro* methodology as screens for detecting chemical-induced immunotoxicity using rodent and human immune cells; develop improved methods for evaluating chemical-induced hypersensitivity and autoimmunity; and develop a testing battery to examine dysfunction in humans occupationally or environmentally exposed to chemicals shown to be immunotoxic in laboratory animals.

In addition to risk assessment, scientists are using the immune system as *in vitro* model systems for studying toxic mechanisms at the cellular and molecular levels. Routine parameters measured in toxicology studies, such as blood or tissue cellularity, are often considerably less sensitive indicators of toxicity than immune function tests. The lymphocyte and macrophage, in particular, possess a number of characteristics that make them an appropriate model for examining the effects of various agents on cell maturation and function. Among these are their capacity to undergo activation *in vitro* in response to antigens or nonspecific stimuli, expression of gene products that can be used as markers of differentiation, the identification and availability of specific growth promoting factors (e.g., interleukins), and their potential to undergo terminal differentiation resulting in produc-

tion of soluble mediators (e.g., monokines, lymphokines, or antibody) or providing effector function (e.g., tumor target cell killing).

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